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EXAMINER	
BASI, NIRMAL SINGH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Ne

Office Action Summary	Application No.	Applicant(s)	
	09/995,225	CHEN ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29 and 41-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29, 41-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-0-0

DETAILED ACTION

1. Amendment filed 5/10/05 has been entered. Applicant has added new claims 57-61 and amended claims 41-45. Newly added claims will be examined together with pending claims 29 and 41-56. IDS filed 5/10/05 has been considered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Applicants arguments:

Applicant argues support for the new amendment to claims 41, 42 and 43 is disclosed in the specification, page 19 nor Table E. Applicant's arguments have been fully considered but are not found persuasive.

3. Claims 41, 43 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 41, 43 and 45 recite "associated with sensorimotor processing or arousal disorder", the specification, page 19 nor Table E support the new subject matter. Table E discloses RUP35 is expressed in the thalamus. Page 19 discloses "The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue

compared to a normal tissue, can be used to correlate location to function and indicate the receptor's physiological role/function and create a treatment regimen, including but

not limited to, a disease associated with that function/role. Receptors can also be localized to regions of organs by this technique. Based on the known or assumed roles/functions of the specific tissues to which the receptor is localized, the putative physiological function of the receptor can be deduced. For example and not limitation, proteins located/expressed in areas of the thalamus are associated with sensorimotor

processing and arousal". The claims require that the isolated polynucleotide encode a GPCR which exhibits expression in the thalamus and (a) is associated with sensorimotor processing or arousal disorder and/or (b) increases an intracellular level of IP3. Although the claimed receptor was isolated in the thalamus there is no disclosure in the specification that the GPCR comprising the amino acid sequence of SEQ ID NO:16 is associated with sensorimotor processing or arousal disorder. The specification discloses the presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be used to correlate location to function and indicate the receptor's physiological role/function and create a treatment regimen, including but not limited to, a disease associated with that function/role. Therefore the association with sensorimotor processing or arousal disorder is not disclosed.

4. Applicant argues the specification provides a specific, substantial and credible utility. Applicant argues:

The specification clearly asserts methods for treating thalamus-related disorders and for direct identification of agonists or inverse agonists applicable as therapeutic agents and in particular those related to sensorimotor processing or arousal. Those of skill in the art, at the time of filing, would have recognized sensorimotor processing disorders include tremor disorders, action tremor disorders, and disorders of impaired motor coordination, and that arousal disorders include impaired cognitive performance. The asserted utility, that RUP35 can be used in treating thalamus-related disorders and for direct identification of therapeutic agents therefor. Further, the asserted utility is specific to thalamus-related disorders, particularly those related to sensorimotor processing and/or arousal. The use of RUP35 in treating, or screening candidate compounds for treating thalamus-related disorders is a real-world use. Substantial utility is found where the candidate compound, itself has specific and substantial utility. To have specific and substantial utility, there must be a real-world use for treatment of a specified disease. Here, it is clear that the disease is a disorder associated with the thalamus, particularly sensorimotor processing disorders and/or arousal

disorders. Such disorders are well-known in the art and include tremor disorders, action tremor disorders, disorders of impaired motor coordination, and impaired

cognitive performance, as noted above. RUP35 is a recognized GPCR and that knowledge of a GPCR'S natural ligand is not necessary for establishing the function for such a receptor. The agonists of the so-called niacin receptor have long been recognized and used to raise HDL levels in man, e.g. nicotinic acid and acipomox. The natural ligand for this receptor is still a mystery. Applicants may very likely develop and market modulators of RUP35 without ever knowing the natural ligand. Applicant also argues assertions above with regard to the utility of the present invention is

supported by the Revised Interim Utility Guidelines Training Materials in Example 12.

Applicant's arguments have been fully considered but are not found persuasive. Examiner is not disputing that the claimed invention encodes a GPCR but that said GPCR does not have a specific, substantial and credible utility. Although the claimed receptor has been shown to be expressed in the thalamus there is no disclosure of the specific association with a sensorimotor processing or arousal disorder. The determination of the specific association with a sensorimotor processing or arousal disorder requires further research. Unlike the argued agonists of the niacin receptor no agonists or antagonists of RUP35 are disclosed which can be used to support a specific, substantial and credible utility. Again the determination of said ligands and their specific use requires further research. Unlike the niacin receptor agonist which can be used to raise HDL levels in man no agonists or antagonists are disclosed for RUP35 which have a specific use such as raising HDL levels. When the claimed GPCR is

compared to Example 12 of Revised Interim Utility Guidelines Training Materials said GPCR has no specific disclosed function or specific ligands that can be used to support utility. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed hRUP35 further experimentation is necessary to attribute a utility to the claimed hRUP35. The instant application does not disclose the biological role of hRUP35 or its significance. The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the hRUP35 of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, applicants claimed invention is incomplete.

Claim Rejection, 35 U.S.C. 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 41-43, 46-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41, 43 and 45, are indefinite because it is not clear what is the association of the G-protein coupled receptor to sensorimotor processing or arousal disorder so as to allow the metes and bounds of the claims to be determined.

Claims 42 and 46-56 are indefinite because they depend on an indefinite base claim and fail to resolve the issues raised above.

The rejection of record of claims 29, 41-56 under 35 U.S.C. 101 and first paragraph of 35 U.S.C. 112 is maintained and newly added claims are rejected for the reasons given below.

Claim Rejections - 35 USC 101 and 35 USC 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the

same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 29, 41-61 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

A Aspecific utility is a utility that is specific to the subject matter claimed, as opposed to a general utility that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well established utility" is a utility that is well known, immediately apparent, or implied by the specifications disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A Awell established utility must also be specific and substantial as well as credible.

Based on the record, there is not a "well established utility" for the claimed invention. Applicant has asserted utilities for the specifically claimed invention of claims 29, 41-56. The invention is directed to a polynucleotide, SEQ ID NO:15, encoding a human G protein coupled receptor comprising hRUP35 SEQ ID NO:16, vector comprising said polynucleotide, and host cell comprising said plasmid. The specification contains numerous polynucleotides encoding various G protein coupled receptors (GPCR). The specification gives generic uses to many of the GPCRs, suggested uses are: direct identification of candidate

compounds as receptor agonists, inverse agonists or partial agonists having potential applicability as therapeutic agents, receptor screening, disease/disorder identification and/or selection, medicinal chemistry and in pharmaceutical compositions. The specification discloses general functional activities of G-protein coupled receptors (GPCR) which may be applicable to G-protein coupled receptors but does not disclose any specific activity, associated with the hRUP35 of instant invention. Figure 2 discloses 293 cells expressing hRUP35 have higher levels of IP3, as compared to control cells not expressing hRUP35, but the significance of this observation as it relates to utility under 35 USC 101 has not been disclosed. Further two primers (SEQ ID NOs 64 and 65) hybridize to hRUP35 in the thalamus. No ligands that bind or activate hRUP35 are disclosed. The specification discloses that hRUP35 of the present invention may be a member of the GPCR protein family. In light of the specification the skilled artisan can only speculate that hRUP35 of instant invention is a protein belonging to the GPCR protein family. However, no disclosure is provided within the instant specification on what specific function a putative hRUP35 protein possesses, or ligands that bind, promoters that activate; nor are any cell types/tissues disclosed that specifically express this protein; nor are any disease states disclosed that are directly related to hRUP35 dysfunction.

Mudroch et al (Review Article attached, see previous Office Action) discloses, the superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant

molecules, and even photons and calcium ions (page 3032, introduction). Members of a sub-family of G-protein-coupled receptors are also highly divergent in their effects, as highlighted by Mudroch et al, in the discussion of cytokine G-protein-coupled receptors (see pages 3032-3039). The utility of hRUP35 cannot be implicated solely from homology to known G-protein coupled receptors because the art does not provide teaching stating that all members of a sub-family of G-protein coupled receptors must have the same effects, the same ligands and be involved in the same disease states, the art discloses evidence to the contrary. For example, Mudroch et al discloses even though CCR6 is a member of the chemokine G-protein coupled receptors family and IL-2 was shown to up-regulate CCR6 mRNA recent data contradict this finding, and as a consequence, the effect of IL-2 on CCR6 expression remains uncertain (page 3035, second column, first paragraph). The hRUP35 of instant invention is considered by the examiner to be a member of the orphan receptor of G-protein coupled receptors i.e. seven transmembrane receptor with no known endogenous ligands. Applicants also classify hRUP35 as an orphan receptor. Watson et al (see previous Office Action) devote a whole chapter to orphan G-protein coupled receptors and group them separately because even though the orphan receptors posses a certain degree of homology to G-protein coupled receptors with known function, the orphan receptors require further research before they can be classified into one of the groupings of known G-protein coupled receptors (Watson et al, pages 223-230). Further, a position that the hRUP35 is related, through homology, to known orphan receptors may be true,

but the art shows it requires more than the disclosed homology to assign a function to an orphan receptor, knowledge of the endogenous ligand for the receptor is required. The assumption that an orphan receptor be placed in a particular group is not always true as highlighted by the statement Watson, who states, Alt was originally claimed that the human homologue of RDC1 codes for VIP receptor, but this is no longer thought to be correct (page 228).

The specification discloses general functional activities of GPCRs which may be applicable to claimed hRUP35 but does not disclose any activity associated with the specific hRUP35. Also, ligands that bind hRUP35 may not interact, with other GPCRs in the same manner or even have the same effect.

The utilities asserted by Applicant are not specific or substantial. Since no specific function of the polypeptide of instant invention is known, and the hypothesized function is based entirely on conjecture from homologous polypeptides, the asserted utilities are not specific to instant polypeptide, but rather are based on family attributes. Neither the specification nor the art of record disclose the hRUP35 fragments or variants thereof useful to identify drugs that affect said protein and modulate its activity. Similarly, neither the specification nor the art of record disclose any instances where disorders can be effected by interfering with the activity using the hRUP35, fragments or variants thereof. Thus the corresponding asserted utilities are essentially methods of using hRUP35 to identify disease states associated with hRUP35 dysfunction, as targets for drug discovery or further research upon itself. Therefore the asserted utilities are essentially methods of testing for or for potentially treating

unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with hRUP35 which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a Areal world≅ context of use for the claimed hRUP35 further experimentation is necessary to attribute a utility to the claimed polypeptides and fragments thereof. See Brenner v. Manson, 383 U.S. 519, 535B36, 148 USPQ 689, 696 (1966) (noting that ACongress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use-testing, and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed hRUP35 further experimentation is necessary to attribute a utility to the claimed hRUP35. The instant application does not disclose the biological role of hRUP35 or its significance. The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the hRUP35 of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After

further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are Auseful≅ to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of Auseful≅ as it appears in 35 U.S.C.101, which requires that an invention must have either an immediately apparent or fully disclosed Areal world utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

Claims 29 and 41-56 are drawn to a polynucleotide encoding a polypeptide with, as yet, undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the hRUP35 as of the filing date, useful for Adiagnosis, prevention, and

treatment of disease, such as cancers etc. Until some actual and specific significance can be attributed to the protein identified in the specification as hRUP35, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or real world utility as of the filing date.

The cDNA of the instant invention and the protein encoded thereby are compounds which share some structural similarity to receptor proteins having GPCR domains based on sequence similarity. As disclosed by the specification, the family of proteins related to hRUP35 may have diverse effects and bind a diverse number of ligands. The family of proteins having GPCR like domains has different levels of expression, and play roles in the pathogenesis of various diseases. Although the family of receptor proteins having GPCR like domains may share some common structural motifs, various members of the family may have different sites of action and different biological effects. In the absence of knowledge of the ligand for hRUP35 or the biological significance of these proteins, there is no immediately evident patentable use. To employ a protein of the instant invention in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible real world use for hRUP35 then the claimed invention as disclosed does not meet the requirements of 35 U.S.C.101 as being useful.

Neither the specification nor the art of record disclose hRUP35 or fragments thereof useful to identify drugs that affect said protein and modulate its activity. Similarly, neither the specification nor the art of record disclose any instances where disorders can be effected by interfering with the activity using hRUP35. Thus the corresponding asserted utilities are essentially methods of using hRUP35 to identify disease states associated with HRUP35 dysfunction and as targets for drug discovery. Therefore the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with hRUP35 which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed hRUP35 , further experimentation is necessary to attribute a utility to the claimed hRUP35 . Further since the nucleic acid encoding hRUP35 receptor or the encoded polypeptide are not supported by either a specific and substantial asserted utility or a well established utility, it follows that the methods of using hRUP35 are also not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above

Further, with regard to diagnosis of disease, in order for a polypeptide or protein to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed

polypeptide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA or protein and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polypeptide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of the claimed polypeptide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the polynucleotide or the claimed polypeptide that is encoded thereby and any disease or disorder and the lack of any correlation between the polynucleotide or the encoded claimed polypeptide with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. Congress intended that no patent be granted on a chemical compound whose sole >utility= consists of its potential role as an object of use-testing *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

Further, the rejection is based on the failure to disclose sufficient properties of the protein and/or polynucleotide to support an inference of utility. hRUP35 belongs is a family in which the members have divergent functions. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family.

The diversity of the biochemical function and the wide range of regulatory pathways involving GTP-binding proteins are well known in the art. Without some common biological activity for the family members, a new member would not have a specific, substantial, or credible utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for toxicology testing, diagnosis is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound,

if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use. Further, the specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. If the expression of the claimed hRUP35 increases, is this a positive or negative outcome? Would this be a toxic response or not? The disclosure is insufficient to evaluate the results of the test in any meaningful manner.

Without knowing a biological significance of the claimed polynucleotide or its encoded polypeptide, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible Areal world≅ manner based on the diversity of biological activities possessed by GTP-binding proteins. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one

skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The implication that the claimed invention has utility in toxicology testing, drug development and disease diagnosis, do not meet the standards for a specific, substantial, and credible or well-established utility for reasons set forth above.

Further, Applicant infers that a utility may be specified even if it applies to a broad class of inventions. The proposition is not sufficient to establish utility for each member of the class. Specific utility must be shown or be evident for each member of the class. None of the utilities identified by Applicant, i.e. toxicology testing, drug discovery, disease diagnosis, have been demonstrated to be specific to the compounds of hRUP35 . One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of HRUP35

In all cases a practical utility of an invention may be derived from belonging to a broad class of inventions. The requirement in any particular case, however, is that practical utility can be inferred if each and every member of the broad class possesses a common utility. The question in the instant application is whether the members of the family of proteins to which the claimed invention is structurally related have, individually, a specific, substantial and credible or well-established utility. Applicant has failed to show by a preponderance of the evidence, in enough detail, with respect to the described hRUP35 has any

substantial use. The record shows that the GTP-binding protein family is diverse, and has such a broad definition, that a Acommon utility cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

7. Claims 29 and 41-61 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a Areal world context of use for the claimed cDNA encoding hRUP35 further experimentation is necessary to attribute a utility to the claimed polypeptides and fragments thereof.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention. A review of *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance

presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the whether undue experimentation would be required to use the claimed invention. As is evidence in the discussions *supra*, each of these factors has been carefully considered in the instant grounds of rejection, and it is maintained that undue experimentation would be required by the skilled artisan to use the instant invention.

The specification implies that the use of the claimed invention for toxicology testing, drug discovery, and disease diagnosis are substantial utilities. The question at issue is whether or not the broad general assertion that the claimed nucleic acids might be used for *some* diagnostic application in the absence of a disclosure of *which* diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to

show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.)

The specification implies that since instant invention has some sequence homology to known orphan receptors that a reasonable correlation has been established and the asserted utility must be accepted. However, for reasons set forth above, the specification or prior art has not presented sufficient evidence to support specific utility for hRUP35. The present rejection under 101 follows *Brenner v. Manson*, as set forth above. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. As Applicant recognizes, a rejection under 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 20 00); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

Further claims 44-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 44-45 and 57-61 are drawn to an isolated polynucleotide, wherein said polynucleotide comprises a nucleic

acid sequence encoding an endogenous human G protein-coupled receptor, said nucleic acid sequence being obtainable by a process comprising performing polymerase chain reaction (PCR) on a human cDNA sample using a primer that consists of the nucleotide sequence

set forth in SEQ ID NO:41 and a primer that consists of the nucleotide sequence set forth in SEQ ID NO:42. Claims 46-56 are drawn to vectors comprising the polynucleotide of claim 45, recombinant host cell containing said vector and isolated membrane of said recombinant cell. Instant fact pattern closely resembles that in Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1992). In Ex parte Maizel, the claimed invention was directed to compounds which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The disclosed compound in both the instant case and in Ex parte Maizel was the full length, naturally occurring protein. The disclosed compound in instant application is a primer SEQ ID NO:41 (27 nucleotides) and SEQ ID NO:41 (25 nucleotides) which do not even encode the full length polypeptide. The critical feature of the invention as it relates structure to function is not contained in the primer sequence. In Ex parte Maizel the Board found that there was no reasonable correlation between the scope of exclusive right desired by Appellant and the scope of enablement set forth in the patent application. Even though Appellant in Ex parte Maizel urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are "conservative" and do not modify the basic functional

equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation. Clearly, a single disclosed sequence does not support claims to any nucleic acid isolated by the process of claims 44 and 45, given the lack of guidance regarding what sequences would hybridize specifically to sequence complementary to the polynucleotide of SEQ ID NO:41 and 42 and not other, related sequences. Further, many of the polypeptides encoded by the nucleic acids isolated will be unrelated to the protein of SEQ ID No:16, being devoid of its characteristic structural and functional features. The claims encompass any fusion construct comprising the primers SEQ ID NO:41 and 42 encoding a fusion construct with or without the ability to increase IP3 levels by interaction with unknown compounds in a cell. For example G-protein coupled receptors associated with Go and Gq activation of the enzyme phospholipase C will have an effect on IP3, this includes the orphan receptors. The specification does not disclose how to use the unrelated compounds isolated by claimed method. Further, many compounds isolated may be inactive. The specification does not disclose how to use inactive compounds. Inactive compounds may be truncated polynucleotides devoid of function and lacking the critical feature that relates structure to function. Due to the large quantity of experimentation necessary to identify the polypeptides with the structural and functional features of instant invention, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polynucleotides, the unpredictability of the effects of

mutation on the structure and function of proteins (since mutations of SEQ ID NO:15 and 16 are also encompassed by the claim), and the breadth of the claim which fail to recite meaningful structural and functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

As is evidence in the discussions *supra*, undue experimentation would be required by the skilled artisan to make and use the instant invention. Further since the claimed hRUP35 has no utility, vector comprising the claimed nucleic acid, cell comprising said vector, composition comprising claimed nucleic acid, membrane isolated from said cell are also rejected under 35 USC 112, 1st paragraph.

Claim Rejection 35 USC ∋ 112, 1st paragraph (Written Description)

8. Claims 44-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 44-61 are drawn to an isolated polynucleotide, wherein said polynucleotide comprises a nucleic acid sequence encoding an endogenous human G protein-coupled receptor, said nucleic acid sequence being obtainable by a process comprising performing polymerase chain reaction (PCR) on a human cDNA sample using a primer that consists of the nucleotide sequence set

forth in SEQ ID NO:41 and a primer that consists of the nucleotide sequence set forth in SEQ ID NO:42. Claims 46-56 are drawn to vectors comprising the polynucleotide of claim 45, recombinant host cell containing said vector and isolated membrane of said recombinant cell.

The claims encompasses polynucleotides that hybridize to two small primers (SEQ ID NOs:41 and 42) and encode a GPCR comprising the amino acid sequence of SEQ ID NO:16 which is associated with sensorimotor processing or arousal disorder and/or increases an intracellular level of IP3. The ability to hybridize to the primers does not disclose the critical feature of the invention that is required for activity for hRUP35. Every polynucleotide known to man can be made to bind to the primers disclosed in claim 44. Most of said polynucleotides will be unrelated to RUP35, structurally and functionally. Claims 45-61 require the nucleic acid to encode an active polypeptide, the specific activity which differentiated claimed invention from other related receptors or polypeptides is not disclosed. All fusion GPCRs constructed to contain sequences complementary to SEQ ID NOs: 41 and 42 will be isolated by the process claimed. Therefore nucleic acid molecules encoding variants of the protein disclosed in SEQ ID NO:16, said variants may be completely unrelated, structurally and functionally to the protein encoded by SEQ ID NO:16 are encompassed by the claims. The common function of the nucleic acid (SEQ ID NO:15) encoding the polypeptide (SEQ ID NO:16), which is based upon a common property or critical technical feature of the genus claimed is not disclosed. The ligand that binds hRUP35 is not disclosed. The claims, as

written, encompass nucleic acid encoding polypeptides which vary substantially in length and also in amino acid composition. The instant disclosure of a polynucleotide of SEQ ID NO:15 encoding the polypeptide of SEQ ID NO:16 does not adequately describe the scope of the use of the claimed genus, which encompasses a substantial variety of subgenera including polynucleotides, variants of said polynucleotides, allelic variants, chimeric constructs, fusion constructs which may encode polypeptides completely, unrelated functionally to the polypeptide of SEQ ID NO:16. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. For example, what regions and fragments of the claimed hRUP35 contain a definitive structural feature required for protein function? The specification proposes to discover other members of the genus by using screening assays and techniques involving probes, primers, and hybridization. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the

compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and proteins encompassed. No identifying characteristic or property of the instant polypeptides/polynucleotide is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific polypeptide and nucleotide sequences and the inability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe, enable and use the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is acknowledged that the skill of the artisan in the molecular biology art is high. However, in the current instance, there is no clear evidence of the specific activity possessed by the claimed genus of nucleic acid molecules encoding variant hRUP35 polypeptides, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the genus claimed relates to function. Because of the lack of

guidance in the prior art and current application, one skilled in the art could not predict if the variants hRUP35 have the same activity as the protein disclosed in SEQ ID NO:16, since no activity is disclosed, or if they contain the domain(s) of SEQ ID NO:16, containing the critical special technical feature of the claimed hRUP35, since no critical special technical feature is disclosed. The specification discloses hRUP35 is an orphan receptor, i.e. Receptor with no known ligand and function

The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115). Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The

nucleic acid or polypeptide is itself is required. See *Fibers v. Revel*, 25 USPQ d. 1601 at 1606 (CAFC 1993) and *Amen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Therefore the specification fails to disclose the activity of the claimed genus of polypeptides/polynucleotides, the critical special technical feature of the polypeptides/polynucleotides or how the critical special technical feature encompassed by the fragments and variants of claimed hRUP35 relates to function.

The claims encompass nucleic acids encoding proteins which are structurally and functionally unrelated to the protein/nucleic acid disclosed in SEQ ID NO:16 and 15, respectively. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of nucleic acids/polypeptides . There is no description of the

conserved regions which are critical to the structure and function of the genus claimed. There is no disclosure of the specific activity of claimed hRUP35 and how it is specifically assayed. Neither specification nor claims disclose the specific activity of the HRUP35 of instant invention or a description of the conserved regions which are critical to the structure and function of the genus claimed.

The claimed nucleic acid encodes an orphan receptor hRUP35 whose activity, associated function and activating ligands have not been disclosed. The neither specification nor prior art provide a specific assay for the genus claimed. The superfamily of GPCRs is specialized proteins designed for chemical recognition of specific ligands and subsequent transduction of information encoded in those ligands/compounds to the machinery of the cell. GPCRs interact with many diverse compounds having diverse effects. The important features which would help to define the hRUP35 activity and define the genus claimed have not been disclosed in the specification nor prior art. Further the activity transduced is not disclosed or how it relates structure to function.

Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of polypeptides/polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The neither specification nor claims disclose the specific activity of the orphan hRUP35 of instant invention, how it is assayed, nor a description of the conserved regions which are critical to the structure and function of the genus

claimed. Further vector comprising the claimed nucleic acid, cell comprising said vector, composition comprising claimed nucleic acid are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi
July 25, 2005

JOSEPH MURPHY
PATENT EXAMINER